ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

COPY

2505 '99 AUG 27 A10:02

SENT VIA UNITED PARCEL SERVICE

Dockets Management Branch
Food and Drug Administration
HFA No. 305, Room No. 1061
5630 Fishers Lane
Rockville, MD 20852

AUG 26 1999

Dear Madam or Sir:

Re: Docket Number 99D-0529

Reference is made to the FDA Draft Guidance for Industry entitled, "Changes to an Approved NDA or ANDA," which was published in the Federal Register on June 28, 1999.

Astra Pharmaceuticals and Zeneca Pharmaceuticals has reviewed this draft guidance; our comments are attached.

Please do not hesitate to contact me should you require clarification on any of the above comments.

Sincerely,

Robert Castor
Assistant Director
Chemistry, Manufacturing and Controls Group
Regulatory Affairs Department
(302) 886-2594
(302) 886-2822 (fax)

RC/CSF/jr
Enclosure

99D-0529

C19

Comments on Draft Guidance "Changes to an Approved NDA or ANDA"

Astra Pharmaceuticals and Zeneca Pharmaceuticals

General Comments

The introduction of the Guidance clearly states that this document is a companion guidance to the changes proposed for 21 CFR 314.70, which has been amended by the Food and Drug Administration Modernization Act (FDAMA). Many of the suggested requirements proposed here are counter to the spirit and literal meaning of FDAMA, which was enacted to provide regulatory relief without compromising quality, safety, or efficacy of drugs.

Section 116 of FDAMA clearly states the situations in which a sponsor will make a change that may have "major" implications for safety or efficacy of the drug substance or product in question. Major changes are clearly stated in the Act as formulation, specification, or bioequivalence changes. These types of post-approval changes require prior approval (PA) from the Agency before the change is implemented. Many of our specific comments are linked to the issue that the Agency has proposed PA supplements for changes that are clearly outside of the 3 major change categories described in FDAMA and/or justification of a proposed change being filed as PA is not provided.

The degree to which a change will likely affect product identity, strength, quality, purity, and potency should be consistently linked to the chance that the proposed change will adversely affect the drug substance or product. The guidance is inconsistent with FDAMA in this area, since many changes that are considered "major", are really "moderate" or "minor" changes and some "moderate" changes are of minor consequence. A few "minor" changes do not require regulatory filings at all.

In addition to discrepancies with FDAMA, this Guidance also is counter to previously published Agency guidances such as SUPAC. If the Agency has already determined that providing regulatory relief via SUPACs and other guidances is acceptable practice, then we respectfully question the reasoning behind changing these same policies back to a more burdensome state.

New regulations pertaining to natural products that appear in the CFR and the Draft Guidance are burdensome to Industry and should be deleted.

The organization of the draft guidance is somewhat confusing. The text flow would be improved if the guidance more clearly delineated requirements for drug substance versus drug product. Dividing the document into drug substance and drug product sections or using a tabular format are two suggestions for improving organization. In addition, there are repetitious areas which could be eliminated. General Considerations Sections for each type of change discussed summarizes categories of regulatory filings which is reiterated in the major, moderate, or minor changes sections which follow. We do find the cross-references, in the Draft Guidance, to the applicable section of the proposed regulation to be helpful.

Specific Comments on Draft Guidance for Industry: "Changes to an Approved NDA or ANDA"

Line	Comments
48 - 78	The guidance allows for a new filing category. The "Supplement—Changes Being Effected in 30 days" (CBE-30) is a favorable change.
82 - 83	Please give a rationale for requiring PA for a comparability protocol. A CBE filing would be less burdensome and Industry could still obtain Agency "buy in" on the protocol before submission of a CBE filing.
89	Cover letters are not appropriate for ARs. Form FDA 2252 is used as the cover letter and table of contents.
101 - 103	This paragraph states that when supplements are filed, a statement certifying that a field copy of the supplement has been provided to the applicant's home district office must be included for US and foreign sites. Historically, we have had specific requests from the FDA to provide additional field copies to the DEIO office. Please clarify whether or not the Agency intends to continue this practice for foreign sites.
145 - 148	When assessing the impact of a change on bioequivalence, the guidance states that "...could include multipoint and /or multimedia dissolution profiling and/or an in vivo bioequivalence study". This is a new, restrictive requirement and is in opposition to the trend toward removal of Case C dissolution (multimedia dissolution) testing described in SUPAC and supported by research at the University of Maryland.
149-151	We suggest providing an appendix listing major reference guidances.
176 - 178	What is the Agency's rationale for requiring PA when a sponsor's degradation qualification procedure indicates that there are no safety concerns or toxicology issues surrounding a change? We suggest a CBE-30 filing when the above stated criteria are fulfilled.
190-191	We believe that changes in formulation, regardless of the intended purpose of the ingredient, are more appropriately addressed in terms of percent change allowed at each level as delineated in the SUPAC Guidances.
198 (footnote 7)	The packaging components (container and closure systems)and their preparation (such as sterilization) are considered to be part of the manufacturing process. This principle is too general and thus, restrictive.
211 - 218	This section describes specific types of changes of site(s) that would be filed as PA. These changes could be scientifically assessed via less burdensome regulatory filings which would be consistent with the spirit and letter of FDAMA, which does not consider site changes "major".
212 - 213	This sentence states that a PA supplement must be filed if, "the facility has never been inspected by the FDA for the type of operations...". Formerly, the regulations provided for a CBE supplement if the new site had a satisfactory GMP inspection within 2 years (and the process in the new facility did not differ materially from the old process). This section effectively removes that provision. We strenuously object to removal of this regulatory relief. We also believe that a CBE filing would suffice for facilities that have never been inspected for a particular process, as well as for facilities with positive GMP inspection history. The CBE filing will trigger the GMP inspection and/or pre-approval inspection (PAI) the same as the PA, but is less burdensome.

Specific Comments on Draft Guidance for Industry: "Changes to an Approved NDA or ANDA"

Line	Comments
214 - 215	Please clarify the meaning of "discontinued" and that areas that are not in production, but intend to be restarted, will not be affected by this. For example, a piece of equipment that is fully validated for a process, but unused for a year, is technically "not in production". It should not require a PA supplement in order to use this equipment for the previously qualified process.
247 - 279	This section lists six different site changes that require PA supplements. This is particularly restrictive since FDAMA does not consider site changes one of the "major" changes that should require PA supplements. We strongly object to the following references in this section and suggest CBE filings instead: • Lines 250-252 (cross reference to lines 214-215) • Lines 253-255 (cross reference to lines 211-218) • Lines 271-276-describes the transfer of an aseptically processed sterile drug substance or product requiring PA. The guidance states that subsequent site changes for similar product types could be filed as a CBE-30. The requirement that the initial change be filed as PA is too restrictive. A CBE filing will trigger a PAI as well as a PA supplement and is more in line with the philosophy stated in the Guidance that subsequent changes could be filed as a CBE-30.
289 - 291	Please clarify if the intent here is to have tighter requirements for site changes that involve sterile drug substances. If so, please provide a rationale. We do not agree that sterile drug substances require tighter requirements for site changes as compared to non-sterile drug substances. Good science practice in validation and technology transfer suffice for either sterile or non-sterile drug substances.
294-300	Please justify why a move to a new testing site on a different campus is listed as a CBE-30. If the provisions listed in lines 294-301 are all met by the applicant and the new testing site, an AR filing would suffice. A move to a new testing site on the same campus (line 317) is annual reportable. The distance involved in the move does not justify a more stringent filing.
303 -309	Please clarify lines 305-309 as being applicable to drug substance intermediates other than the final intermediate. This section describes the move to a new site for manufacturing or processing drug substance intermediates, including the final intermediate, and the requirement for a CBE filing. We suggest an AR filing, even if the contract manufacturer is not previously approved in the application, as long as the equivalency of impurity profiles and physical properties are proven, as per BACPAC I.
373 - 414	In general, this section is too restrictive. The following changes are suggested: • Line 373-This line is too vague and implies that "all" sterility changes require PA. We suggest deleting this line. • Lines 374, 376, 389, 391, 395, and 411 give examples where the maximum filing requirement should be CBE as none of these situations describe "major" changes according to FDAMA. • Line 380-Adding new equipment to an aseptic processing line is a GMP concern. We recommend deletion of these lines. • Line 386-Changes in lyophilization equipment is a GMP concern. We recommend deletion of these lines.

Specific Comments on Draft Guidance for Industry: "Changes to an Approved NDA or ANDA"

Line	Comments
373 - 414	• Line 398-This line describes load pattern changes which is a GMP concern. We recommend deletion of these lines. • Line 400-Changes to filtration parameters are GMP issues. We recommend deletion of these lines. • Line 414- In some cases, a change in the route of synthesis of a drug substance can be filed as a CBE according to BACPAC I. This Guidance contradicts the regulatory relief outlined in BACPAC I and is overly restrictive.
421 - 423	A change involving an ink not currently used on CDER-approved products is particularly restrictive and results in a PA supplement. Please provide a list of CDER-approved inks or reference to such a list.
435, 438	Changes in depyrogenation are "minor", therefore, annual reportable. Filtration parameters such as flow rate, pressure, time, or volume are GMP issues and should not be discussed here.
445	Elimination of an in-process filtration system for a terminally sterilized product is described here. Please clarify whether the reason for the in-process filtration system is for particulate matter or for sterility issues. This is a particularly restrictive change if the purpose of the filter is for sterility, since terminal sterilization adequately assures product quality. If this is the case, a change in filtration should not require a filing at all.
457, 462	We suggest an AR filing for changes in manufacturing scale for aseptic products or terminally sterilized products. A CBE filing is overly restrictive.
481-482	Please cross reference this section to SUPAC for clarity.
485 - 487	This section references inks used on CDER-approved products. Please provide a list or cross-reference to a list of approved inks.
491	Does this change in the order of addition of ingredients also apply to solid oral dosage forms?
522-523	Please clarify why a change in an analytical procedure used for testing packaging components is considered to be a major change requiring a PA supplement.
536	Please define "product". Does this mean drug product and drug substance?
558-561	Changes to specifications or methods to *increase* the controls and quality of the drug product should be annual reportable.
559	Please define "drug". Does this refer to drug product and drug substance?
567	This section states that any "change made to comply with an official compendium, *that is consistent with FDA requirements...*" is an AR filing. This statement implies that there may be separate and/or different requirements to fulfill USP and FDA criteria. This situation is burdensome since Industry has always assumed that USP requirements were consistent with FDA thinking. Further, Section 501 (b) of the Federal Food, Drug and Cosmetic Act states that if drug product meets compendial requirements, it is considered unadulterated. Please clarify this statement. Specifically, if the regulation is intended to require PA supplements for deleting or widening a specification due to a change in USP, we disagree with this proposal. Please clarify this issue. We recommend that any change made to comply with an official compendium should be annual reportable.

Specific Comments on Draft Guidance for Industry: "Changes to an Approved NDA or ANDA"

Line	Comments
601	A reference is made to ink and/or adhesive that has not been approved by CDER. Please provide a list or cross-reference to a list of CDER-approved inks and adhesives.
612 - 616 and 617 - 618	Reference is made to packaging components that are CDER approved as well as another reference to approved inks and/or adhesives. Please provide a list or cross-reference to a list of CDER-approved packaging components.
626 - 639	Please justify why this list of sterile product changes are considered "major" changes requiring PA. Some of these examples are GMP considerations. None of these examples are "major changes" according to FDAMA. Provision for PA filings in these cases are contrary to the spirit and intent of FDAMA.
647	We suggest that no filing is required for a change in a secondary packaging components that are not intended to provide additional product protection and does not impact labeling (see also line 711).
651 - 652	This change in container size and/or shape for nonsterile drug product is too restrictive as a CBE filing and should be allowed via AR.
657-660	Please clarify if this section covers changes from one type of material to another (i.e. from glass to plastic) or only covers changes within a category of material construction (i.e. from one plastic to another).
661 - 662	This section describes a change in the size and shape of a container containing the same number of dose units. Please address the case where the number of dose units are changed but the container size and/or shape remains the same.
666-667	Please provide a reference for industry to obtain information on primary packaging component materials that have been used in CDER-approved solid oral dosage form products.
652, 662, 667, 681, 696, 700	Is "solid dosage form" the same as "solid oral dosage form" in this context? Different terminology is used in these lines. It is unclear if this is intentional or a discrepancy. Please clarify.
668-682	Are desiccants or absorbing materials also covered in this section?
679	How do you know which antioxidants, stabilizers, or mold releasing agents for production of the container and /or closure system are used with CDER-approved products? Please provide a reference.
689	This line states that the material in contact with liquid topical products should already be used in CDER-approved liquid topical products. Please provide a reference to a list of CDER-approved materials to be used with liquid topical products.
695	Are changes in the pocket dimensions of the individual blister packs covered in this statement? Please clarify.
711	We suggest that no filing is required for a change in a secondary packaging components that are not intended to provide additional product protection and does not impact labeling (see also line 647).

Specific Comments on Draft Guidance for Industry: "Changes to an Approved NDA or ANDA"

Line	Comments
776	This line describes changes that affect product sterility assurance. This statement is too vague and requires clarification or deletion.
778	The example of a comparability protocol seems out of place here. The comparability protocol and its recommended filing were covered in lines 82-83. Again, we object to the comparability protocol approval requiring PA, since a CBE filing would be less burdensome and Industry could still obtain Agency "buy in" on the protocol before submission of a CBE filing (see lines 82-83).
779-781	See Lines 790-792 below.
790-792	The extension of an expiration dating period based upon full shelf-life data on full production batches is restrictive. FDAMA provides for the use of pilot scale batches to demonstrate safety and effectiveness of the drug; ICH also approves of using pilot scale batches for approval of expiry dating. Additionally, the Draft Guidance, "Stability Testing of Drug Substances and Drug Products" state that pilot scale batches may be used for tentative approval and extension of expiry dating. We believe that use of pilot scale batches to confirm an expiry date is scientifically justifiable and that this should be apparent in the regulation and in related guidances.
863	This definition of "secondary packaging component" clearly states that the component(s) in question do not have product contact, which supports our contention that changes to secondary packaging which do not provide additional product protection and do not impact labeling, should not require regulatory action (see comment lines 711-713).

YAIR®

AK

With UPS you can count on fast, reliable air service
and around the world. Choose from
to meet your need

We make it easy f
options, including
service centers.

Around-the-clock pa
are two more ways w
1-800-PICK-UPS (1-8

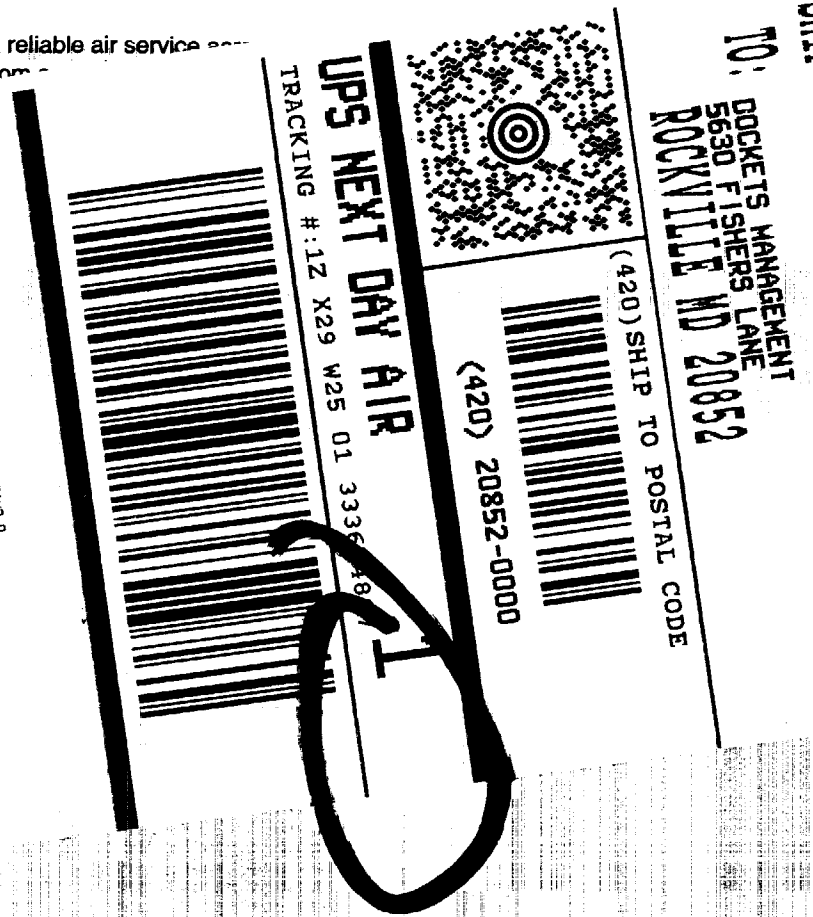
Please separate your

Place Labels in This Space

Options: 1 UPS Tracking Label and your address label – Place the Tracking Label to
2 UPS Air Shipping Document
3 UPS Waybill

ZENECA Pharmaceuticals

A business unit of Zeneca Inc.
Drug Regulatory Affairs Department
1800 Concord Pike
Wilmington, DE 19850-5437



SHIP
TO: DOCKETS MANAGEMENT
5630 FISHERS LANE
ROCKVILLE MD 20852

ZENECA PHARMACEUTICALS
302 886-1298
1800 CONCORD PIKE
WILMINGTON DE 19803

1 LBS 1 OF 1

Dockets Management Branch
Food and Drug Administration
HFA No. 305, Room No. 1061
5630 Fishers Lane
Rockville, MD 20852